Guidance for Industry

FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products

DRAFT GUIDANCE - NOT FOR IMPLEMENTATION

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Comments and suggestions regarding this draft document should be submitted by May 30, 1997, to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number 97D-0099. For questions regarding this draft document, contact Robert L. Delap (CDER), 301-594-2473 or Patricia Keegan (CBER), 301-827-5097.

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GUIDANCE FOR INDUSTRY:[1] FDA APPROVAL OF NEW CANCER TREATMENTUSES FOR MARKETED DRUG AND BIOLOGICAL PRODUCTS

I. INTRODUCTION

FDA has launched a *"New Use Initiative — Evidence for Primary and Supplemental Approvals"* to explore steps the Agency can take to improve the process for approving promising new uses for drug and biological products. This new initiative is based on FDA's belief that when products approved for one use are shown to be safe and effective for treating other conditions, those new uses should be added to product labeling as soon as possible.

Unfortunately, sponsors often are reluctant to submit applications for supplemental new uses for their drug and biological products. There may be a perception that revising product labeling to add new uses (which requires submission and FDA approval of a supplemental marketing application) is difficult, costly, and time-consuming. FDA believes it can improve its supplemental approval process and increase the number of safe and effective new uses being added to drug labeling (1) by clarifying what evidence should be provided for primary as well as supplemental applications and (2) by working with industry to reduce barriers to submitting applications for new uses for their products.

This guidance for industry considers the quality and quantity of data that may be adequate to add a new use to the prescribing information for a product used in the treatment of cancer. It

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[1] This guidance has been prepared by the Division of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration with input from the Supplemental Indications Working Group, an Agency working group headed by the Deputy Commissioner for Operations. This guidance document represents the Agency's current thinking on FDA approval of new cancer treatment uses for marketed drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For additional copies of this guidance, contact (1) the Drug Information Branch, Division of Communications Management, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-827-4573), or (2) the Office of Communication, Training and Manufacturers Assistance, HFM-40, CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist that office in processing your requests. The document may also be obtained by mail by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800, or by fax by calling the CBER FAX Information System at 1-888-CBERFAX or 301-827-3844. An electronic version of this guidance is also available via Internet using the World Wide Web (WWW). To access the document on the WWW, connect to (1) the CDER Home Page at WWW.FDA.GOV/CDER and go to the "Regulatory Guidance" section or (2) CBER at http://www.FDA.gov/CBER/cberftp.html.

describes steps FDA is taking to foster the updating of labeling for products used in cancer treatment. The information provided here should be considered in conjunction with a more general Agency document addressing related issues, entitled, "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products."

II. BACKGROUND

Product labeling is intended to provide full prescribing information for a product and should include all clinical indications for which adequate data are available to establish the product's safety and effectiveness. However, many newer uses of anticancer products that are common in clinical practice and appear to be supported by published data from clinical studies are not included in product labeling, despite the incentives sponsors have to keep their product labeling updated with information about new uses.

There are a number of incentives for holders of approved marketing applications to submit supplemental applications for new uses for their marketed products. These incentives include (1) the desire to provide patients and physicians with the best, most recent information about scientifically established uses of a product, (2) increased sales as a result of being able to promote a product for additional clinical indications, and (3) the greater likelihood of reimbursement by third-party insurance payers. There are also disincentives, including (1) the effort and cost involved in completing new research (where necessary) to determine whether a product provides patient benefit in a new indication; (2) the effort and cost involved in submitting an application for regulatory approval of new clinical uses; and (3) the lack of perceived commercial benefit of revised labeling if the product is already used for the new indication, especially if it no longer has patent protection.

Applicants interested in submitting supplemental marketing applications should not be discouraged by exaggerated perceptions of the data that should be submitted to label a product for a new anticancer indication. Nor should they be discouraged by the misperception that the Agency considers such applications to be of relatively little importance.

As part of FDA's efforts to encourage supplemental submissions, this guidance document has been developed to discuss the nature of the data that should be submitted in support of an application for the approval of a new indication for products currently marketed for cancer treatment. It also describes other steps FDA is taking to foster continued updating of labeling for anticancer products. The principles and standards relevant to establishing a new anticancer use for a marketed product also are applicable to establishing the initial use(s) of a new product in an original marketing application.

III. ADDING INDICATIONS TO PRODUCT LABELING

To add new use information to the labeling of a marketed product, a holder of an approved marketing application must submit a supplemental marketing application that provides data that establishes the safety and effectiveness of the product for the proposed new indication (21 CFR 314.70). The application should include all relevant data available from pertinent clinical studies, including negative or ambiguous results as well as positive findings. To support approval, the data submitted should be sufficient in quality and quantity to establish the safety and effectiveness of the product with a high level of confidence, as required by law and scientific expectations.

Sponsors conducting research on products for use in treating cancer patients are strongly encouraged to consult with the Agency for specific advice on study designs and product development plans, especially prior to initiating resource-intensive or marketing application-directed studies.

A. Clinical Data to Support Product Effectiveness and Safety in a New Indication

The amount and types of new data to be provided in a supplemental marketing application depend as much on the quality of the new data as on what already is known about the product and the proposed new use of the product. (See "Draft Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.") Results of prior clinical studies of a product can be used to support the findings of subsequent clinical studies.

The types and quantity of clinical data that should be provided to support a new use for a product will vary depending on the cancer indication under study and the availability and acceptability of other therapies. In the refractory cancer setting, for example, where no therapies are available with meaningful benefit, nonrandomized studies showing that a new treatment provides a significant objective response rate with tolerable treatment toxicity may be sufficient to support approval under the accelerated approval regulations. Study findings are more persuasive when such studies are performed at multiple centers, with consistency of results across centers, and when the number of patients enrolled is sufficient to obtain a reliable estimate of the response rate. Observation of complete objective remissions of significant duration in a significant proportion of patients enrolled in nonrandomized studies can support the conventional approval of a new product use. On the other hand, observations of palliation of tumor-related symptoms or of improved survival duration or a lengthening in time to disease progression generally are deemed reliable if they are found in randomized studies that include a concurrent control group and are adequate in size to allow analysis of the primary study endpoint(s). In the adjuvant setting, where all known tumor has been effectively treated (e.g. by surgical removal) and many or most patients may enjoy long-term survival without a recurrence even with no further therapy, risks of serious treatment toxicities are much less acceptable, and relatively large randomized studies are typically necessary to assess the benefits and risks of a new treatment.

As indicated in the "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," the additional clinical data to be provided to support a new use of an already-marketed product may be less extensive since existing controlled trial data may provide additional support for the new use. Examples of the clinical data that should be provided to establish effectiveness and safety of a product in a new cancer indication are as follows[2]:

1. If a product has already been shown to be safe and effective in the treatment of patients with a given type of cancer, a single, adequate and well-controlled, multicenter study demonstrating acceptable safety and effectiveness in another biologically similar form of cancer that is known to have a generally similar pattern of responsiveness to chemotherapy may support labeling for that additional form of cancer. For example, if a product is currently approved for use in treatment of advanced squamous carcinomas of the head and neck and approval for use in treatment of another advanced aerodigestive squamous carcinoma is sought (e.g., squamous lung cancer or esophageal cancer), a single, adequate and well-controlled, multicenter study may be sufficient.[3]

   Similarly, if a product already has been shown to be acceptably safe and effective in treatment of patients with a given type of solid tumor malignancy in advanced, refractory stages, then a single, adequate and well-controlled, multicenter study in patients with another type of advanced, refractory solid tumor (with a response rate endpoint, and enrollment of sufficient patients to estimate response rate with adequate precision) may be sufficient to support approval for treatment of this additional type of tumor.

2. If a product already has been shown to be acceptably safe and effective in treatment of a given type of cancer in adults, then the additional data needed to establish acceptable safety and effectiveness of the product in children with that same type of cancer may be limited (as long as the effects of the drug and the type of cancer under study appear to be biologically similar in children and adults). A

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[2] In each example, it is assumed that clinical trials are adequately designed and well-conducted, that trial outcomes are favorable, and that data from other studies do not contradict the observed favorable results. In some settings, trials that do not include a concurrent, randomized control group may still be adequate and well-controlled clinical trials, with patients serving as their own controls. Conversely, clinical trials that include a concurrent control group may not always constitute adequate and well-controlled trials (e.g. if there are serious deficiencies in the design or conduct of a study or the selected control group is not appropriate).

[3] In this document *approval* may indicate either conventional approval or accelerated approval, depending on the specific cancer indication under study, study endpoints, and the details of the study findings.

single, multicenter study establishing the safety of the product in children, typically with pharmacokinetic data that can be compared with pharmacokinetics findings of previous studies in adults and including efficacy observations, will usually be sufficient.[4] In disease settings where established curative treatments are available for children, a randomized, controlled trial of ethically and scientifically appropriate design (with a survival and/or time to progression endpoint, depending on the exact circumstances) may be necessary.

3. For a product used to ameliorate an adverse effect of a cancer treatment, there is often concern that the product could also significantly reduce the effectiveness of the cancer treatment. In such cases, when the product has been shown to ameliorate adverse treatment effects without significantly compromising the palliative effectiveness of treatment for patients with one specific type of cancer, it usually will be labeled for use only in that type of cancer. However, a single, additional, adequate and well-controlled, multicenter study that demonstrates that the product can similarly reduce adverse treatment effects in patients with a second type of cancer (again, without reducing the palliative effectiveness of cancer treatment) may be sufficient to support labeling of the product for use to ameliorate adverse treatment effects in all similar palliative settings with labeling that excepts only settings where treatment is known to be potentially curative or is associated with a substantial survival benefit. In those settings, where preservation of effectiveness is particularly important, additional studies usually would be needed.

4. New dosing regimens (including changes in the range of doses administered for approved indications, and in the schedule of administration) can lead to improved effectiveness, tolerance, or convenience. A single, adequate, and well-controlled study demonstrating the safety and effectiveness of the product when administered for an approved indication using a different dosing regimen will generally be sufficient to support the addition of the new dosing regimen to product labeling.

5. If a product already has been shown to be acceptably safe and effective for treatment of patients with a given type of cancer in advanced, refractory stages, support for a claim in an earlier stage of the same type of cancer may be provided by a single, adequate and well-controlled, multicenter study demonstrating acceptable safety and effectiveness. For example, for a product that is already

[4] This reflects the current FDA CDER/CBER "Guidance for Industry regarding the Content and Format for Pediatric Use Supplements." See the CDER section of the FDA World Wide Web home page. See also final rule, 59 *Federal Register* 64240, December 13, 1994.

approved for treatment of metastatic colorectal cancer or breast cancer (refractory or second-line), a single, randomized, controlled trial (with a survival or carefully assessed time to disease progression endpoint) could be sufficient to support approval for initial (front-line) treatment of the same condition.

6. If a product already has been shown to be acceptably safe and effective as part of a combination treatment regimen for a given type of cancer, then a single, adequate and well-controlled study providing evidence of safety and effectiveness when administered alone in the same clinical setting may be sufficient to support the addition of the new monotherapy dosing regimen to product labeling.

Similarly, if a product already has been shown to be acceptably safe and effective when administered alone in the treatment of a given type of cancer, then a single, adequate and well-controlled study providing evidence of safety and effectiveness of the product when administered together with other products that have established safety and effectiveness in treatment of that condition will generally be sufficient to support the addition of the new combination dosing regimen to product labeling.

7. If the safety/toxicity profile of a product has been well established in prior studies, the safety data needed to support additional clinical indications for the product would be limited, provided that the product is administered in a similar fashion when used in the additional indications.

8. Depending on the data available from prior studies, applications for new uses of a product typically do not require additional data regarding pharmacokinetics (PK); concomitant medications and possible drug-drug interactions; or evaluation of product safety as a function of age, gender, race, or co-existing diseases.

All of these examples are intended to illustrate in a general way the quantity and types of data that should be provided to support typical labeling changes. However, the specific data needs may vary substantially from case to case, depending on what is already known about the product and the specific cancer indications under study. Sponsors are strongly encouraged to consult with the Agency for specific advice on the design of research programs intended to support new product labeling before proceeding with such programs.

B. Alternative Sources of Clinical Study Data

Although clinical studies conducted by pharmaceutical companies generally are carefully

monitored, are subjected to quality control audits, and can achieve very high quality, alternative approaches, such as those described below, also may provide reliable data to support the effectiveness and safety of a product in cancer treatment. For example, most of the data pertaining to the adjuvant therapy of breast and bowel cancers have come from studies performed independently of pharmaceutical companies (See "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.") Some examples of alternative approaches to data gathering are provided here.

1. Data, including individual patient data, study reports, and statistical analyses may be obtained from experienced, independent cancer clinical trials organizations that have well-established and publicly available procedures for research data management, monitoring, and auditing, and a track record of high-quality research (e.g., U.S. National Cancer Institute-sponsored cooperative cancer research groups or other highly credible organizations that have no commercial interest in study outcomes). Such data can be submitted to FDA without additional data collection, auditing, or analyses by a pharmaceutical company submitting a supplemental marketing application as long as (1) the clinical trials organization can provide the data necessary for FDA to check and verify all major study findings (e.g. stratification and randomization data, and tumor measurements in studies that use objective response rate as a primary efficacy variable) and (2) the clinical trials organization is willing to work with FDA to resolve any issues that may arise during FDA review.

Although these organizations usually do not carry out the monthly on-site monitoring that is often performed in company-sponsored studies, they do have established audit procedures. FDA has had extensive experience in the review of data and analyses from such independent organizations during the past several years and has found the data and the analyses to be generally highly credible and reliable.

2. In situations where reports of controlled studies from multiple centers, published in adequate detail in peer-reviewed journals, provide consistent support for the effectiveness and safety of a product in a cancer indication, such reports may form the primary basis to establish the safety and effectiveness of a product in a cancer indication. The centers and investigators generating these data should have substantial experience in clinical cancer investigations and no commercial interest in the study outcomes.

In most circumstances, such literature reports should be supplemented by selected additional information (e.g., copies of study protocols, data tapes giving relevant baseline and outcome information, and/or case records of individual patients reported as having critical efficacy or safety findings). These types of additional information are generally readily obtainable with minimal effort and expense for recently conducted studies and may substantially enhance the usefulness of a study in supporting product labeling. A single published report supplemented by such additional information may be persuasive.

The general request for this additional information is based on prior experiences where, following review of study records, FDA has sometimes been unable to confirm major findings of published studies (including multicenter studies published in high-quality, peer-reviewed journals). However, if favorable results have been reported from several well-controlled studies, published in peer-reviewed journals by different groups of investigators, only some (and in certain cases, none) of this additional information may be needed.

IV. FDA INITIATIVES TO MAINTAIN UPDATED LABELING FOR PRODUCTS USED IN CANCER TREATMENT

Treatment of many forms of cancer is in continuous evolution due to the efforts of many researchers in the private, academic, and government sectors. After a product receives initial marketing approval, it will be used in a variety of settings, especially where available treatments are unsatisfactory. Product labeling, therefore, may not include the very latest information about promising new uses for products, and in many cases, early promise is not borne out by subsequent definitive studies. It is important, however, for the labeling of products used in cancer treatment to include information on all scientifically proven uses. FDA has made a number of efforts to enhance the quality of labeling for products currently approved for use in cancer treatment. Additional efforts are planned:

1. In the past, FDA has surveyed private, academic, and professional groups involved in cancer research and treatment for their views regarding appropriate uses of products in cancer treatment that are not described in current product labeling. Where appropriate, FDA has met with commercial sponsors of marketed products and has encouraged the submission of supplemental marketing applications. FDA will continue to survey major groups in the cancer research and treatment community for their views regarding new cancer treatment indications that should be examined for possible inclusion in labeling for currently marketed products.

FDA also will consider proposals from any source regarding promising new cancer treatment indications that should be examined for possible inclusion in labeling. Proposals may be submitted by paper mail. FDA also will provide for the submission of such proposals by electronic mail, through the Internet/World Wide Web. In all of these cases, reference to supportive clinical data will be extremely helpful.

2. FDA plans to institute a program in which Agency professional staff regularly review the labeling of each product used in cancer treatment to consider whether there are uses or dosing regimens that appear to be well supported by the results of clinical studies, but are not yet included in labeling.

3. Whenever FDA identifies important product uses or dosing regimens that may be well supported by the results of clinical studies, but not yet included in labeling, the Agency will contact the commercial sponsor(s) of the product and encourage the sponsor(s) to evaluate the available data and, if the data appear adequate, to submit a supplemental marketing application.

4. In the event that commercial sponsors of a product do not respond to an FDA request to evaluate the data regarding a currently unlabeled indication for a product used in cancer treatment, FDA may pursue other avenues, depending on specific circumstances and in accordance with applicable laws and regulations. For example, FDA may provide public notification of the Agency's interest in receiving a supplemental application for review from any interested applicant. Alternatively, the Agency may seek summation and analysis of the data by staff of other governmental agencies (e.g., staff of the National Cancer Institute), for review by FDA staff. In some instances, FDA may seek to obtain study data for summaries and analysis by Agency staff.

5. A special assistant will be appointed in the Division of Oncology Drug Products of the Center for Drug Evaluation and Research and in the Oncology Branch of the Division of Clinical Trial Design and Analysis of the Center for Biologics Evaluation and Research to monitor, track, and manage the progress of all efforts to maintain updated product labeling for all products used in cancer treatment. This will include managing efforts to

seek the views of major groups and of individuals in the cancer research and treatment community, management and monitoring of actions regarding possible labeling revisions, and preparation of regular progress reports.